

Amendments to the Claims:

Please amend claims 18, 41, 42, 67, 99, and 117

These amendments introduce no new matter and support for the amendment is replete throughout the specification and claims as originally filed. These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter, or agreement with any objection or rejection of record.

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1. (Original) A method of screening for a test agent that modulates dimer/heterodimer formation or cofactor interaction with a nuclear receptor, the method comprising:
 - contacting at least one nuclear receptor dimer/heterodimer regulatory site (DHRS)
 - of at least one nuclear receptor with a test agent; and,
 - detecting a change in a level of dimer/heterodimer formation or a change in cofactor interaction with the at least one nuclear receptor that is mediated by the test agent, thereby screening for the test agent that modulates dimer/heterodimer formation or cofactor interaction with the nuclear receptor.
2. (Original) The method of claim 1, wherein the at least one DHRS comprises a hydrophobic cluster, and wherein the hydrophobic cluster is located on a surface of the nuclear receptor.
3. (Original) The method of claim 2, wherein the at least one DHRS further comprises a region comprising polar and non-polar amino acids proximal to the hydrophobic cluster.
4. (Original) The method of claim 3, wherein the at least one DHRS further comprises a solvent-based region.
5. (Original) The method of claim 1, wherein the at least one DHRS comprises residues Valine 376, Leucine 400, Leucine 422, and Valine 425 of a thyroid hormone receptor β .

6. (Original) The method of claim 5, wherein the at least one DHRS further comprises residues Serine 381, Aspartate 382, Glutamate 393, Glutamate 396, and Arginine 429 of the thyroid hormone receptor β .
7. (Original) The method of claim 6, wherein the at least one DHRS further comprises a solvent-based region.
8. (Original) The method of claim 1, wherein the at least one DHRS comprises residues Valine 322, Leucine 346, Leucine 368, and Valine 371 of a thyroid hormone receptor α .
9. (Original) The method of claim 1, wherein the at least one DHRS comprises residues Alanine 381, Valine 405, Leucine 427, and Methionine 430 of a peroxisome proliferator activated α receptor.
10. (Original) The method of claim 1, wherein the at least one DHRS comprises residues Valine 390, Leucine 414, Leucine 436, and Methionine 439 of a peroxisome proliferator activated γ receptor.
11. (Original) The method of claim 1, wherein the at least one DHRS comprises residues Isoleucine 332, Leucine 356, Leucine 378, and Isoleucine 381 of a retinoic acid α receptor.
12. (Original) The method of claim 1, wherein the at least one DHRS comprises residues Isoleucine 346, Alanine 370, Methionine 394, and Leucine 397 of a pregnane X receptor.
13. (Original) The method of claim 1, wherein the at least one DHRS comprises residues Isoleucine 336, Serine 360, Isoleucine 384, and Leucine 387 of a vitamin D receptor.
14. (Original) The method of claim 1, wherein the at least one DHRS comprises residues Leucine 810, Isoleucine 835, Threonine 860, and Leucine 863 of an androgen receptor.
15. (Original) The method of claim 1, wherein the at least one DHRS comprises residues Isoleucine 451, Threonine 483, Leucine 508, and Leucine 511 of an estrogen receptor.
16. (Original) The method of claim 1, wherein the at least one DHRS comprises residues Leucine 824, Isoleucine 849, Threonine 874, and Leucine 877 of a progesterone receptor.

17. (Original) The method of claim 1, wherein the agent masks residues in the at least one DHRS of the at least one nuclear receptor, thereby preventing dimer/heterodimer formation.

18. (Currently amended) The method of claim 1, wherein the at least one nuclear receptor is selected from the group consisting of: a steroid hormone receptor, a thyroid hormone receptor, a glucocorticoid receptor, an estrogen receptor, an androgen receptor, a mineralocorticoid receptor, a progestin receptor, a vitamin D receptor, a retinoid receptor, a retinoid X receptor, a peroxisomal proliferator activated receptor, an estrogen-receptor related receptor, a short heterodimer partner, a constitutive androstane receptor, a liver X receptor, a pregnane X receptor, a HNF-4 receptor, a farnesoid X receptor, and an orphan receptor.

19. (Original) The method of claim 1, further comprising:

comparing a change in a level of dimer/heterodimer formation of the at least one nuclear receptor to a level of dimer/heterodimer formation in a control, wherein a difference in the level of dimer/heterodimer formation in the contacted DHRS and the level in the control indicates that the agent alters dimer/heterodimer formation of the at least one nuclear receptor.

20. (Original) The method of claim 19, wherein the control is exposed to a lower concentration of the test agent.

21. (Original) The method of claim 20, wherein the lower concentration is the absence of said test agent.

22. (Original) The method of claim 1, wherein the agent modulates an interaction of the at least one nuclear receptor and a cofactor molecule.

23. (Original) The method of claim 1, wherein the change in the level of dimer/heterodimer formation or the change in cofactor molecule interaction correlates with an activation of the at least one nuclear receptor.

24. (Original) The method of claim 1, wherein the change in the level of dimer/heterodimer formation or the change in cofactor molecule interaction correlates with a repression of the at least one nuclear receptor activity.

25. (Original) The method of claim 1, wherein the level of dimer/heterodimer formation or the change in cofactor molecule interaction is detected by detecting expression of at least one nuclear receptor responsive gene or reporter gene.

26. (Original) The method of claim 1, wherein the level of dimer/heterodimer formation or the change in cofactor molecule interaction is detected by detecting nuclear receptor activation.
27. (Original) The method of claim 1, wherein the level of dimer/heterodimer formation or the change in cofactor molecule interaction is detected by detecting nuclear receptor repression.
28. (Original) The method of claim 1, wherein the level of dimer/heterodimer formation or the change in cofactor molecule interaction is detected by a gel shift assay, a fluorescence assay, a chromatography assay, an immunochemistry assay, a fusion tag assay, or a two hybrid assay.
29. (Original) The method of claim 1, wherein the at least one nuclear receptor comprises at least two nuclear receptors.
30. (Original) The method of claim 29, wherein one of the at least two nuclear receptors is a retinoid X receptor (RXR).
31. (Original) The method of claim 1, wherein the test agent is an agent other than an antibody.
32. (Original) The method of claim 1, wherein the test agent is an agent other than a protein.
33. (Original) The method of claim 1, wherein the test agent is a small organic molecule.
34. (Original) The method of claim 1, wherein the test agent is a peptide.
35. (Original) The method of claim 1, wherein the test agent is contacted directly to the at least one DHRS.
36. (Original) The method of claim 1, wherein the test agent is contacted to a cell containing the at least one DHRS.
37. (Original) The method of claim 1, wherein the test agent is contacted to an animal comprising a cell containing the at least one DHRS.

38. (Original) The method of claim 1, wherein detecting the change mediated by the test agent is performed in vitro.
39. (Original) The method of claim 1, wherein detecting the change mediated by the test agent is performed in vivo.
40. (Withdrawn) A nuclear receptor: agent complex produced by the method of claim 1.
41. (Currently amended) The complex of claim 40, wherein the agent is 3, 5-dimethyl-4-(4'-hydroxy-3'-benzyl)benzyl-phenoxy acetic acid (GC-24).
42. (Currently amended) The complex of claim 40, wherein the agent is an agent other than 3, 5-dimethyl-4-(4'-hydroxy-3'-benzyl)benzyl-phenoxy acetic acid (GC-24).
43. (Withdrawn) A method of treating a subject having a disease state which is alleviated by treatment with a nuclear receptor modulator, the method comprising administering a therapeutically effective amount of an agent of claim 1 to the subject in need thereof.
44. (Withdrawn) The method of claim 43, wherein the disease state is selected from the group consisting of: hyperthyroidism, aldosteronism, Cushing's syndrome, hirsutism, cancer, thyroid cancer, breast cancer, prostate cancer, bone cancer, ovarian cancer, hypercholesterolemia, hyperlipidemia, atherosclerosis, obesity, cardiac arrhythmia, modulation of reproductive organ function, hypothyroidism, osteoporosis, hypertension, glaucoma, and depression.
45. (Withdrawn) The method of claim 43, wherein the agent is mixed with one or more pharmaceutically acceptable excipients prior to said administering.
46. (Withdrawn) The method of claim 43, wherein the subject is a human.
47. (Withdrawn) The method of claim 43, wherein the subject is a non-human mammal.
48. (Withdrawn) The method of claim 43, wherein the agent is co-administered with an agonist or an antagonist of a nuclear receptor.

49. (Withdrawn) The method of claim 48, wherein the co-administration of the agent and the agonist or the antagonist of the nuclear receptor counteracts at least one deleterious effect of the agonist or the antagonist.
50. (Withdrawn) A method of prescreening for an agent that modulates dimer/heterodimer formation or cofactor molecule interaction of a nuclear receptor, the method comprising:

contacting a nuclear receptor dimer/heterodimer regulatory site (DHRS) with a test agent; and,

detecting a specific binding of the test agent to said DHRS.
51. (Withdrawn) The method of claim 50, wherein the specific binding indicates that the test agent is a candidate modulator of dimer/heterodimer formation or cofactor molecule interaction.
52. (Withdrawn) The method of claim 50, wherein the test agent is not an antibody.
53. (Withdrawn) The method of claim 50, wherein the test agent is not a protein.
54. (Withdrawn) The method of claim 50, wherein the test agent is a small organic molecule.
55. (Withdrawn) The method of claim 50, wherein the test agent is a peptide.
56. (Withdrawn) A method of designing a compound to contact a nuclear receptor dimer/heterodimer regulatory site (DHRS), the method comprising:

providing a three dimensional model of a protein or polypeptide comprising the DHRS; and,

modeling a binding of one or more compounds to the three dimensional model, thereby identifying one or more compound that binds to the DHRS.
57. (Withdrawn) The method of claim 56, wherein modeling of the binding comprises using a computer program to design a putative compound that binds to the DHRS.
58. (Withdrawn) The method of claim 57, wherein the computer program is selected from the group consisting of: DOCK, Catalyst and MCSS/Hook.
59. (Withdrawn) A nuclear receptor:bound compound complex produced by the method of claim 56.

60. (Withdrawn) The complex of claim 59, wherein the complex inhibits or reduces dimerization or heterodimerization of the nuclear receptor.
61. (Withdrawn) The complex of claim 59, wherein the complex inhibits or reduces binding of one or more cofactor molecules to the nuclear receptor.
62. (Withdrawn) The complex of claim 59, wherein the complex inhibits an appropriate folding of the ligand binding domain of the nuclear receptor.
63. (Withdrawn) The complex of claim 59, wherein the complex inhibits activation of an AF-1 domain of the nuclear receptor.
64. (Withdrawn) A method of identifying one or more modulators for at least one nuclear receptor, the method comprising:
- providing a plurality of putative modulators;
 - contacting at least one nuclear receptor dimer/heterodimer regulatory site (DHRS) of a nuclear receptor with the putative modulators, wherein at least one of the putative modulators binds the DHRS; and,
 - testing the putative modulators for modulator activity on the nuclear receptor, thereby identifying the one or more modulators of the nuclear receptor.
65. (Withdrawn) The method of claim 64, wherein the plurality of putative modulators comprises between 5 and 1000 members.
66. (Withdrawn) The method of claim 64, wherein the plurality of putative modulators comprises more than 1000 members.
67. (Currently amended) The method of claim 64, wherein the nuclear receptor is selected from the group consisting of: a steroid hormone receptor, a thyroid hormone receptor, a glucocorticoid receptor, an estrogen receptor, an androgen receptor, a mineralocorticoid receptor, a progesterone receptor, a vitamin D receptor, a retinoid receptor, a retinoid X receptor, a peroxisomal proliferator activated receptor, an estrogen-receptor related receptor, a short heterodimer partner, a constitutive androstane receptor, a liver X receptor, a pregnane X receptor, a HNF-4 receptor, a farnesoid X receptor, and an orphan receptor.
68. (Withdrawn) The method of claim 64, wherein the testing comprises:

binding the plurality of putative modulators to the least one DHRS;
selecting members of the plurality of putative modulators that bind the at least one DHRS; and,
testing the resulting bound nuclear receptor for modulator activity.

69. (Withdrawn) The method of claim 64, wherein the modulator activity is nuclear receptor activation.

70. (Withdrawn) The method of claim 64, wherein the modulator activity is repression of nuclear receptor activity.

71. (Withdrawn) The method of claim 64, wherein the modulator activity is a dimerization or heterodimerization activity.

72. (Withdrawn) The method of claim 64, wherein the testing is performed in vitro.

73. (Withdrawn) The method of claim 64, wherein the testing is performed in vivo.

74. (Withdrawn) A method of modulating nuclear receptor activation, the method comprising:

contacting a nuclear receptor dimer/heterodimer regulatory site (DHRS) of a nuclear receptor with an agent; wherein the agent preferentially binds the DHRS, thereby modulating nuclear receptor activation.

75. (Withdrawn) The method of claim 74, wherein the DHRS comprises a hydrophobic cluster and is located on the surface of the nuclear receptor.

76. (Withdrawn) The method of claim 75, wherein the DHRS further comprises a region comprising polar and non-polar amino acids proximal to the hydrophobic cluster.

77. (Withdrawn) The method of claim 76, wherein the DHRS further comprises a solvent-based region.

78. (Withdrawn) The method of claim 74, wherein the DHRS comprises residues corresponding to Valine 376, Leucine 400, Leucine 422 and Valine 425 of a thyroid hormone receptor β .

79. (Withdrawn) The method of claim 78, wherein the DHRS further comprises residues Serine 381, Aspartate 382, Glutamate 393, Glutamate 396, and Arginine 429 of the thyroid hormone receptor β .
80. (Withdrawn) The method of claim 79, wherein the DHRS further comprises a solvent-based region.
81. (Withdrawn) The method of claim 74, wherein the DHRS comprises residues Valine 322, Leucine 346, Leucine 368, and Valine 371 of a thyroid hormone receptor α .
82. (Withdrawn) The method of claim 74, wherein the DHRS comprises residues Alanine 381, Valine 405, Leucine 427 and Methionine 430 of a peroxisome proliferator activated α receptor.
83. (Withdrawn) The method of claim 74, wherein the DHRS comprises residues Valine 390, Leucine 414, Leucine 436 and Methionine 439 of a peroxisome proliferator activated γ receptor.
84. (Withdrawn) The method of claim 74, wherein the DHRS comprises residues Isoleucine 332, Leucine 356, Leucine 378 and Isoleucine 381 of a retinoic acid α receptor.
85. (Withdrawn) The method of claim 74, wherein the DHRS comprises residues Isoleucine 346, Alanine 370, Methionine 394 and Leucine 397 of a pregnane X receptor.
86. (Withdrawn) The method of claim 74, wherein the DHRS comprises residues Isoleucine 336, Serine 360, Isoleucine 384 and Leucine 387 of a vitamin D receptor.
87. (Withdrawn) The method of claim 74, wherein the at least one DHRS comprises residues Leucine 810, Isoleucine 835, Threonine 860, and Leucine 863 of an androgen receptor.
88. (Withdrawn) The method of claim 74, wherein the at least one DHRS comprises residues Isoleucine 451, Threonine 483, Leucine 508, and Leucine 511 of an estrogen receptor.
89. (Withdrawn) The method of claim 74, wherein the at least one DHRS comprises residues Leucine 824, Isoleucine 849, Threonine 874, and Leucine 877 of a progesterone receptor.
90. (Withdrawn) The method of claim 74, wherein the agent modulates activation of the nuclear receptor by inhibiting dimer or heterodimer formation of the nuclear receptor.

91. (Withdrawn) The method of claim 74, wherein the agent masks residues in the DHRS and prevents dimer/heterodimer formation, thereby modulating nuclear receptor activation.
92. (Withdrawn) The method of claim 74, wherein the agent modulates nuclear receptor activation by inhibiting activation of an AF-1 domain.
93. (Withdrawn) The method of claim 74, wherein the agent modulates nuclear receptor activation by activating an AF-1 domain.
94. (Withdrawn) The method of claim 74, wherein the agent modulates nuclear receptor activation by inhibiting activation of a liganded nuclear receptor.
95. (Withdrawn) The method of claim 74, wherein the agent modulates nuclear receptor activation by activating a liganded nuclear receptor.
96. (Withdrawn) The method of claim 74, wherein the agent modulates nuclear receptor activation by inhibiting activation of a unliganded nuclear receptor.
97. (Withdrawn) The method of claim 74, wherein the agent modulates nuclear receptor activation by activating a unliganded nuclear receptor.
98. (Withdrawn) The method of claim 74, wherein the agent modulates gene transcription.
99. (Currently amended) The method of claim 74, wherein the nuclear receptor is selected from the group consisting of: a steroid hormone receptor, a thyroid hormone receptor, a glucocorticoid receptor, an estrogen receptor, an androgen receptor, a mineralocorticoid receptor, a progestin receptor, a vitamin D receptor, a retinoid receptor, a retinoid X receptor, a peroxisomal proliferator activated receptor, an estrogen-receptor related receptor, a short heterodimer partner, a constitutive androstane receptor, a liver X receptor, a pregnane X receptor, a HNF-4 receptor, a farnesoid X receptor, and an orphan receptor.
100. (Withdrawn) The method of claim 74, wherein the nuclear receptor comprises a nuclear receptor isoform.

101. (Withdrawn) A nuclear receptor modulator complex comprising a nuclear receptor bound to an agent, wherein the agent preferentially binds a nuclear receptor dimer/heterodimer regulator site (DHRS) of the nuclear receptor.

102. (Withdrawn) The nuclear receptor modulator complex of claim 101, wherein the DHRS comprises a hydrophobic cluster and is located on the surface of the nuclear receptor.

103. (Withdrawn) The nuclear receptor modulator complex of claim 102, wherein the DHRS further comprises a region comprising polar and non-polar amino acids proximal to the hydrophobic cluster.

104. (Withdrawn) The nuclear receptor modulator complex of claim 103, wherein the DHRS further comprises solvent-accessible region.

105. (Withdrawn) The nuclear receptor modulator complex of claim 101, wherein the DHRS comprises residues corresponding to Valine 376, Leucine 400, Leucine 422 and Valine 425 of a thyroid hormone receptor β .

106. (Withdrawn) The nuclear receptor modulator complex of claim 105, wherein the DHRS further comprises residues Serine 381, Aspartate 382, Glutamate 393, Glutamate 396, and Arginine 429 of the thyroid hormone receptor β .

107. (Withdrawn) The nuclear receptor modulator complex of claim 106, wherein the DHRS further comprises a solvent-accessible region.

108. (Withdrawn) The nuclear receptor modulator complex of claim 101, wherein the DHRS comprises residues Valine 322, Leucine 346, Leucine 368, and Valine 371 of a thyroid hormone receptor α .

109. (Withdrawn) The nuclear receptor modulator complex of claim 101, wherein the DHRS comprises residues Alanine 381, Valine 405, Leucine 427 and Methionine 430 of a peroxisome proliferator activated α receptor.

110. (Withdrawn) The nuclear receptor modulator complex of claim 101, wherein the DHRS comprises residues Valine 390, Leucine 414, Leucine 436 and Methionine 439 of a peroxisome proliferator activated γ receptor.

111. (Withdrawn) The nuclear receptor modulator complex of claim 101, wherein the DHRS comprises residues Isoleucine 332, Leucine 356, Leucine 378 and Isoleucine 381 of a retinoic acid α receptor.

112. (Withdrawn) The nuclear receptor modulator complex of claim 101, wherein the DHRS comprises residues Isoleucine 346, Alanine 370, Methionine 394 and Leucine 397 of a pregnane X receptor.

113. (Withdrawn) The nuclear receptor modulator complex of claim 101, wherein the DHRS comprises residues Isoleucine 336, Serine 360, Isoleucine 384 and Leucine 387 of a vitamin D receptor.

114. (Withdrawn) The nuclear receptor modulator complex of claim 101, wherein the at least one DHRS comprises residues Leucine 810, Isoleucine 835, Threonine 860, and Leucine 863 of an androgen receptor.

115. (Withdrawn) The nuclear receptor modulator complex of claim 101, wherein the at least one DHRS comprises residues Isoleucine 451, Threonine 483, Leucine 508, and Leucine 511 of an estrogen receptor.

116. (Withdrawn) The nuclear receptor modulator complex of claim 101, wherein the at least one DHRS comprises residues Leucine 824, Isoleucine 849, Threonine 874, and Leucine 877 of a progesterone receptor.

117. (Currently amended) The nuclear receptor modulator complex of claim 101, wherein the nuclear receptor is selected from the group consisting of: a steroid hormone receptor, a thyroid hormone receptor, a glucocorticoid receptor, an estrogen receptor, an androgen receptor, a mineralocorticoid receptor, a progestin receptor, a vitamin D receptor, a retinoid receptor, a retinoid X receptor, a peroxisomal proliferator activated receptor, an estrogen-receptor related receptor, a short heterodimer partner, a constitutive androstane receptor, a liver X receptor, a pregnane X receptor, a HNF-4 receptor, a farnesoid X receptor, and an orphan receptor.

118. (Withdrawn) The nuclear receptor modulator complex of claim 117, wherein the nuclear receptor comprises a nuclear receptor isoform.

119. (Withdrawn) The nuclear receptor modulator complex of claim 101, wherein the complex is in vitro.

120. (Withdrawn) The nuclear receptor modulator complex of claim 101, wherein the complex is in vivo.

121. (Withdrawn) The nuclear receptor modulator complex of claim 101, wherein the complex is in a cell.

122. (Withdrawn) The nuclear receptor modulator complex of claim 101, wherein the complex is in a mammal.

123. (Withdrawn) A library of modulators for a nuclear receptor, wherein the library comprises a plurality of different modulators that specifically bind a nuclear receptor dimer/heterodimer regulator site (DHRS) of a nuclear receptor.

124. (Withdrawn) The library of claim 123, wherein the library comprises between about 5 and 1000 members.

125. (Withdrawn) The library of claim 123, wherein the library comprises more than about 1000 members.

126. (Withdrawn) The library of claim 123, wherein the library comprises a phage display library.

127. (Original) A screening system for screening test agents that modulate dimer/heterodimer formation or cofactor molecule interaction of nuclear receptors, the screening system comprising:

at least one polypeptide, wherein the at least one polypeptide comprises a nuclear receptor dimer/heterodimer regulatory site (DHRS); and,

instructions for detecting dimer/heterodimerization or interactions of cofactor molecule of the at least one polypeptide.

128. (Original) The screening system of claim 127, wherein the at least one polypeptide comprise a full or partial nuclear receptor amino acid sequence.

129. (Original) The screening system of claim 127, wherein the at least one polypeptide is provided by a nucleic acid, wherein the nucleic acid encodes the at least one polypeptide.

130. (Withdrawn) A prescreening system for prescreening a test agent that bind to a nuclear receptor dimer/heterodimer regulator site (DHRS), the prescreening system comprising:

a polypeptide that comprises the DHRS; and,

instructions for detecting specific binding of the test agent to the DHRS.

131. (Withdrawn) A system for designing putative compounds that contact a nuclear receptor dimer/heterodimer regulatory site (DHRS), the system comprising:

a three dimensional model of a protein or polypeptide comprising a nuclear receptor dimer/heterodimer regulatory site (DHRS); and,

instructions for modeling binding of one or more compounds to the three dimensional model to design at least one putative compound that contacts the DHRS.